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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,640	01/10/2002	Carlo Brugnara	I3691-002005 / 470-104US2	7466
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Gregory P. Einhorn Fish & Richardson P.C. Suite 500 4350 La Jolla Village Drive San Diego, CA 92122			EXAMINER RAO, DEEPAK R	
			ART UNIT 1624	PAPER NUMBER

DATE MAILED: 03/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/043,640	Applicant(s) Brugnara et al.	
	Examiner Deepak Rao	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.

- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.

- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.

- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on Dec 17, 2002

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-16 are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-16 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some* c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). <u>6</u>	6) <input type="checkbox"/> Other: _____

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DETAILED ACTION

Claims 1-16 are pending in this application.

Election/Restriction

Applicant's election of Group I, claims 1-16 drawn to compounds of formula (I) wherein X is C, in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without** traverse (MPEP § 818.03(a)).

Election of a single disclosed species was also required in the previous office action, however, applicant has not provided an election of the species.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of arteriosclerotic diseases, does not reasonably provide enablement for treatment of all types of cancers and **prevention** of any of the diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

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It is disclosed in the specification (page 8, lines 26+) that the instantly claimed compounds are useful in ‘preventing’ various types of disorders characterized by unwanted or abnormal cell proliferation, which include an array of cancerous and non-cancerous conditions. However, the specification fails to provide sufficient evidence that the entire scope of the instantly claimed genus would be effective *in-vivo* in ‘prevention’ of the claimed treatments.

First, note that at pages 52-57, *in vitro* assays and results are provided only for mitogenic and Gardos Channel assays, however, the disorders characterized by abnormal cell proliferation include ‘prevention’ of cancer such as brain cancer, pancreas cancer etc. No assays or results are provided with regards to the activity towards prevention of any type of cancer and, thus, the showing is not commensurate in scope with the claims. Note that in cases involving physiological activity, “the scope of enablement varies inversely with the degree of unpredictability of the factors involved.” *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable *in-vivo* physiological activities, any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds.

Second, there is no evidence on record which demonstrates that the *in-vitro* and *in-vivo* screening tests relied upon are recognized in the art as being reasonably predictive of success in any of the contemplated areas of prevention. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as “showing” such

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utility, and not “warranting further study”). The evidence presented in this case does not show such utilities, but only warrants further study.

Third, note that claim 23 specifically recites ‘preventing a condition’ and in the subsequent dependent claim 26, one option of the condition is identified as “cancer”. However, it is not recited what type of cancer is intended and further, prevention of cancer traditionally has been very difficult or impossible effectively with chemopreventives. See e.g., Omenn, Cecil Textbook of Medicine, 20th Edition (1996), where it is stated that “[s]eemingly logical approaches must be tested in randomized, clinical preventive trials before their merits are accepted” (page 1010). Further, there are no examples of such prevention of ‘cancers’ in the prior art, either in closely or more distantly related compounds. Since such would not be considered conventional, there is no predictability evident for preventing disease states. There is no guidance or direction, nor are there working examples evident that speak to this unconventional modality of dealing with cancers.

Further, no compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a “silver bullet” is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that “each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study” (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163

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USPQ 689 (CCPA 1969), wherein ‘evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers’. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers or abnormal cell proliferative disorders generally.

Further, the scope of the claims includes not only treatment but also ‘**prevention** of a disorder’ which is not adequately enabled solely based on the antiproliferative activity of the compounds provided in the specification. “To prevent” actually means *to anticipate or counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the “prevention” effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein. Next, applicant’s attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that ‘a claimed invention must have a specific and substantial utility’. The disclosure in the instant case is not sufficient to enable the instantly claimed ‘preventive’ effect solely based on the inhibitory activity disclosed for the compounds.

Therefore, since the scope of the claims includes treatment of all types of cancers and/or **prevention** of many disorders, and since there are no examples or guidance for practicing this invention, one of skill in the art would have had born undue burden of experimentation to

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practice the claimed invention at the time the invention was made. In view of the extreme difficulties that have been and are still being encountered in the treatment and/or prevention of cancers, such utilities are unbelievable on their face and therefore they must be supported by sufficient evidence demonstrating such utilities.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In the claims, the definitions of the variables include the terms "(C₁-C₆) alkenyl" and "(C₁-C₆) alkynyl" groups (all occurrences, see e.g., definition of Y, R and R') wherein it is not clear what is intended by a 'C₁ alkenyl or alkynyl' group. An 'alkenyl' or 'alkynyl' is a group having a carbon to carbon double or triple bond and in the instant case, it is not clear what is an alkenyl or alkynyl group having one carbon atom. The specification provides ethenyl, etc. as examples which groups have at least two carbon atoms.
2. Claims 2, 5, 8 and 12 do not show the structural formulae of the compounds in the claims and only the reference numerals are recited. A claim to be complete, must recite all the limitations within the claim or should refer to another claim in which those limitations are recited.

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3. Claim 5 recites the limitation "compound 1" in line 3. There is insufficient antecedent basis for this limitation in the claim. Compound no. 1 is an indolyl compound, i.e., compound of formula (I) wherein X is N. Claims 8 and 12 also include 'compound 1'. *(Handwritten mark)*

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Koelsch, Chem. Abstract 55:48596. The instantly claimed compounds read on the compounds of the reference, see the compounds disclosed in the abstract. The reference also teaches that the compounds exist in water, which is a pharmaceutically acceptable excipient or carrier.

2. Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Starnes, Chem. Abstract 69:43555. The instantly claimed compounds and the corresponding composition read on the reference disclosed compound, see the compound having RN 16778-13-5 in the enclosed copy of CAPLUS computer search report.

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3. Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Morgan, U.S. Patent No. 3,546,165. The instantly claimed compound reads on the reference compound - 1,1-bis(4-hydroxyphenyl)-indane, see col. 4, line 11.

4. Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Barili et al., Chem. Abstract 107:58774. The instantly claimed compound reads on the reference compound RN 104563-21-5, see the enclosed copy of the computer search report.

5. Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Manning et al., Chem. Abstract 94:102538. The instantly claimed compound reads on the reference compounds: RN 18636-52-7, 52033-61-1, 52033-63-3, 75948-91-3, 75948-87-7 and 75961-47-6, see the enclosed copy of the computer search report (the last compound on page 94).

6. Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Enokida et al., Chem. Abstract 126:39836 (JP 08259936, Pub. Date 10/8/1996). The instantly claimed compound reads on the reference compound RN 113505-06-9, see the enclosed copy of the computer search report (the last compound on page 55).

7. Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Enokida et al., Chem. Abstract 126:39836 (JP 08259936, Pub. Date 10/8/1996). The instantly claimed compound reads on the reference compound RN 113505-06-9, see the enclosed copy of the computer search report (the last compound on page 21).

8. Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosnati et al., Chem. Abstract 110:153506. The instantly claimed compounds read on reference disclosed

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compounds, see the enclosed copy of the computer search report and various inden-2-one compounds.

9. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Gagnon, Beilstein Reg. No. 4924895. The instantly claimed compounds read on the reference compound, see the structural formula in the enclosed copy of the computer search report, which is identical to compound no. 4 of claim 2.

10. Claims 1, 3, 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Miller et al., Chem. Abstract 74:75859. The instantly claimed compounds read on the reference disclosed compound, see the compound RN 31366-71-9 in the enclosed copy of the CAPLUS computer search report. The reference teaches the presence of the compound in a solvent and therefore, inherently teaches a composition thereof. The proviso statement in claim 1 has been fully considered but not deemed to be sufficient to overcome the rejection because - the proviso recites 'when X is C and R₁ is -OH, at least one of R₅, R₆ and R₇ is other than -H,...', however, when the subscripts _m and _n are 0 in formula (I) the substituents R₅, R₆ and R₇ are not present and therefore, the claims include the reference disclosed compound.

11. Claims 1, 3, 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Hendrickson et al., Chem. Abstract 110:113878. The instantly claimed compounds read on the reference disclosed compound, see the compound RN 55010-17-8 in the enclosed copy of the CAPLUS computer search report. The reference teaches the presence of the compound in a solvent and therefore, inherently teaches a composition thereof. The proviso statement in claim 1

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has been fully considered but not deemed to be sufficient to overcome the rejection because - the proviso recites 'when X is C and R₁ is =O, at least one of R₅, R₆ and R₇ is other than -H,...', however, when the subscripts _m and _n are 0 in formula (I) the constituents R₅, R₆ and R₇ are not present and therefore, the claims include the reference disclosed compound.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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Claims 6-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 09/880,728*. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims substantially overlap the claims of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Note: PreGrant Pub No. US 2002/0128256 which corresponds to S.No. 09/880,728 is relied upon for the claims of the copending application.*

Receipt is acknowledged of the Information Disclosure Statement filed on June 3, 2002 and a copy is enclosed herewith.

Receipt is also acknowledged of the International Search Report of PCT/US98/24819 and the PTO-892 forms from parent applications and the cited references have been fully considered.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (703) 308-4716. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.


Deepak Rao
Primary Examiner
Art Unit 1624

March 4, 2003